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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/070,220	02/27/2002	Paul L Darke	20511P	9874

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EXAMINER	
LUCAS, ZACHARIAH	
ART UNIT	**PAPER NUMBER**
1648	

DATE MAILED: 07/28/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/070,220	DARKE ET AL.	
	Examiner	Art Unit	
	Zachariah Lucas	1648	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *18 June 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-7,26-28 and 40-44* is/are pending in the application.

4a) Of the above claim(s) *7,26-28 and 42-44* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-5 and 40* is/are rejected.

7)☒ Claim(s) *6 and 41* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *6-11-02*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Election/Restrictions

1. Applicant's election with traverse of Group I, and the subinvention represented by SEQ ID NO: 13, in the reply filed on June 18, 2004 is acknowledged. The traversal is on the ground(s) that the claims are not drawn to compounds, but to methods. This is not found persuasive because, while the claims are not drawn to compounds, the compounds are the common technical feature among the inventions. The inventions are otherwise drawn to methods of performing different functions and having different modes of operation. However, among Groups I, II, and IV, because these methods each has either a different function, or a different mode of operation, it is not clear that there is any common technical feature among these claims. The inventions are still considered to lack a common special technical feature.

The requirement is still deemed proper and is therefore made FINAL.

2. Claims 7, 26-28, and 42-44 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected inventions, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in the reply filed on June 18, 2004.

Information Disclosure Statement

3. The information disclosure statement (IDS) submitted on June 11, 2002, is in compliance with the provisions of 37 CFR 1.97. Accordingly, the information disclosure statement has been considered by the examiner.

Priority

4. It is noted that the present application is a national stage entry of international application PCT/US00/23444, filed on August 25, 2000. It is requested that the first paragraph of the application is amended to reflect this relationship.

Claim Rejections - 35 USC § 112

5. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

6. Claims 1 is rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for methods of inhibiting Hepatitis C virus (HCV) replication using certain peptides comprising certain HCV NS4A sequences, does not reasonably provide enablement for methods using any compound that inhibits NS2/3 autocleavage. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to practice the invention commensurate in scope with these claims. Claim 1 reads on methods of inhibiting HCV replication using any compound that inhibits NS2/3 autocleavage.

In making a determination as to whether an application has met the requirements for enablement under 35 U.S.C. 112 ¶ 1, the courts have put forth a series of factors. See, In re Wands, 8 USPQ2d 1400, at 1404 (CAFC 1988); and Ex Parte Forman, 230 U.S.P.Q. 546 (BPAI 1986). The factors that may be considered include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the

claims. Id. While it is not essential that every factor be examined in detail, those factors deemed most relevant should be considered.

In support of the broad scope of the claims, the application provides examples of certain HCV NS4A peptides that have been shown to inhibit HCV replication to some extent, and provides examples of methods that may be used to screen for other compounds having the required utility. App., pages 15-16, 16-17, and 23-25. However, the application discloses only a limited number of peptides that are so useful, and does not disclose any non-peptide compounds that would be useful in the claimed method. The only guidance provided with respect to non-peptide inhibitors are methods to screen for additional compounds. There is no suggestion as to what other compounds would be likely to have the required utility.

In addition to the lack of guidance in the application, the art also appears to provide limited means by which those in the art would be able to predict which of the many compounds that may be screened would be useful for the practice of the claimed method. The art does however teach that, due to structural features of the HCV protease, those in the art have faced difficulties in the identification of inhibitors thereto. See e.g., Lu et al., Antimicrob Agents Chemother 48: 2260-66, at page 2260, right column. Thus, in addition to the limited guidance provided by the art and application, the art additionally teaches that there is a level of uncertainty and unpredictability in the development of HCV protease inhibitors.

In view of the vast array of compounds that are available for screening, the lack of guidance as to which of these may be able to inhibit NS2/3 cleavage, and the unpredictability in the art, the application has not provided sufficient information to enable those in the art to practice the claimed invention to the full scope as claimed. In order to do so, those in the art

would be required to discover for themselves what other compounds would be useful in the claimed method. The claim is therefore rejected as exceeding the scope of the enabling disclosure provided in the application.

7. Claims 1 and 2 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for methods of inhibiting Hepatitis C virus (HCV) replication using certain peptides comprising certain HCV NS4A sequences, does not reasonably provide enablement for methods using any fragment of the HCV NS4 protein that inhibits NS2/3 autocleavage. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to practice the invention commensurate in scope with these claims. Claim 2 further limits the method of claim 1 (described above) to embodiments wherein the compounds is selected from the group consisting of "an HCV inhibitor polypeptide comprising an NS4A fragment at least about 11 amino acids in length, wherein said fragment can inhibit autocleavage of NS2/3," and salts or prodrugs thereof.

The factors to be considered in making a determination as to whether a claim has met the enablement requirements have been presented above. The current claims read on methods of using any fragment of the NS4 protein that have the ability to inhibit autocleavage of the HCV NS2/3 proteins. However, the only such fragments disclosed in the application are fragments comprising the NS4 target site comprising residues 22-32 of the NS4 protein. Further, both the application and the art (see e.g., Shimizu et al., J Virol 70: 127-132- of record in the June 2002 IDS) indicate that this represents the region of the NS4 protein that associates with the HCV NS3 protein. There is no indication that any other regions of the protein interact with NS2, NS3, or

the uncleaved NS2/3 proteins. The application therefore provides only one example of a NS4A region that would be useful in the claimed invention, and the art and application indicate that other regions would not be likely to be so effective. Thus, while the Applicant may be enabled for the use of NS4A peptide comprising residues 22-31 of the protein, there is insufficient support for claims to the use of any fragment of the NS4A protein.

8. Claims 1 –5 and 40 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for methods of inhibiting Hepatitis C virus (HCV) replication using certain peptides comprising certain HCV NS4A sequences, does not reasonably provide enablement for methods using any compound that inhibits NS2/3 autocleavage, or any peptide within the formula provided as Structure I, on pages 3-4 of the application and in claim 3. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to practice the invention commensurate in scope with these claims. These claims further define the methods described above to embodiments wherein the HCV protease inhibitor is a peptide according to the formula of Structure I.

Structure 1 defines a genus of peptides comprising over 730,000 potential sequences. The application discloses only 5 operative embodiments of these, and each of these 5 comprises the region comprising NS4A residues 21-33 of the HCV-BK NS4A protein as disclosed on page 10 of the application. Thus, while the claim reads on a large genus of peptides, on a limited number of related peptides has been disclosed as useful in the claimed invention.

In addition to the limited number of working examples, the application also discloses that one peptide falling within the scope of the claimed invention, which does not appear to include a

native NS4A sequence, was not operative in the claimed methods. See App., page 24 (disclosing that the peptide of SEQ ID NO: 10 was not able to inhibit replication), and page 25, lines 32-35 (noting that this peptide comprised a "randomized sequence" and was not inhibitory). These teachings both demonstrate that more is required for a peptide to be operative than the presence of a sequence defined by Structure I.

In addition, the art teaches that, while the amino acid sequences of proteins often permit substitutions within their sequences, the effect of a particular substitution is generally not predictable and the effects of multiple substitutions of mutations are additive. See. Bowie et al. Science 247:1306-10 (teachings that while certain positions in a protein sequence may permit any substitution, others that are more closely associated with the function and structure of the protein may permit only limited or no substitutions without a loss of function). See also, Wells, Biochem 29: 8509-17 (teaching the additive effects of protein mutation on protein activity). The art therefore teaches that there is an amount of unpredictability in the manipulation of the protein sequences with respect to their affects on the protein's function. In the present case, the application itself demonstrates that modification of the peptide sequence from those of the native viral sequences reduces, or eliminates, the protease inhibitory function. While the structural formula provides guidance as to what residues may be placed in which positions, the formula places no limitation on the number of variations that may occur from the native sequences. Thus, in view of the unpredictability in the art, the lack of correlation between the Structure I as a whole with the required function, and the demonstration that non-viral derived sequences are likely not to be operative, the application does not provide sufficient enabling support for the use of any peptide falling within the scope of Structure I in the claimed methods.

9. Claims 1-5, and 40 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. The claims have been described above. As indicated above, the claims describe three general groups of inventions. Those wherein the clamed method involves the use of a genus comprising any compound that inhibits NS2/3 cleavage, those that read on the use of any NS4A protein fragment, and those that read on the use of any peptide within the genus described by Structure I.

The following quotation from section 2163 of the Manual of Patent Examination Procedure is a brief discussion of what is required in a specification to satisfy the 35 U.S.C. 112 written description requirement for a generic claim covering several distinct inventions:

> The written description requirement for a claimed genus may be satisfied through sufficient description of a representative number of species by actual reduction to practice..., reduction to drawings..., or by disclosure of relevant, identifying characteristics, i.e., structure or other physical and/or chemical properties, by functional characteristics coupled with a known or disclosed correlation between function and structure, or by a combination of such identifying characteristics, sufficient to show the applicant was in possession of the claimed genus... See Eli Lilly, 119 F.3d at 1568, 43 USPQ2d at 1406.
>
> A "representative number of species" means that the species which are adequately described are representative of the entire genus. Thus, when there is substantial variation within the genus, one must describe a sufficient variety of species to reflect the variation within the genus.

Thus, when a claim covers a genus of inventions, the specification must provide written description support for the entire scope of the genus. Support for a genus is generally found where the applicant has provided a number of examples sufficient so that one in the art would recognize from the specification the scope of what is being claimed.

With respect to the first group of inventions, those that read on the use of any compound that inhibits NS2/3 cleavage, there is no structural component to the claimed genus. Rather, the claimed methods describe the active compound only with reference to the intended function of the compounds. Further, as was indicated above, the application discloses only a limited number of compounds that may be useful in the claimed invention. Each of these disclosed compounds is a peptide. However, while there is some variation among the disclosed peptides (page 24) that are effective, there is not clear correlation between any particular structure, and the operability of the peptide in the claimed method. Nor is there any disclosure of any compound that is not a peptide that would be effective in the claimed methods. The application therefore provides insufficient descriptive support for the first claimed genus of inventions.

The second and third genera of claimed methods relate to methods wherein the compound is a fragment of the HCV NS4A protein, or a peptide according to the function of Structure 1. In the application, the Applicant has provided several examples of such fragments and peptides that have the required function to be operable in the claimed methods. However, in each instance, these disclosed peptides share a common feature; they each comprise residues corresponding to the region of residues 21-33 of an NS4A protein. Cf., App. page 10, Table 1 (disclosing peptides according to the indicated region of the NS4A protein); and page 24, Table 2 (disclosing "NS4a-Derived Peptides," which also fall within the scope of structure I, that would appear to be operative in the claimed methods). There is no disclosure of any other region of the NS4A protein which could be used in the claimed methods. Nor is there any demonstration of any other peptide according to Structure I, other than those comprising the NS4A sequence described above, have the requisite function. Rather, the sole example of peptides having a

structure not comprising the NS4A sequence was found to be inoperative. Thus, the information presented by the Applicant demonstrates a correlation between the sequence of residues 21-33 of the NS4A protein and the HCV protease inhibition activity. There is no evidence that any NS4A fragment, or any peptide according to Structure 1 have this function.

Thus, while the Applicant has asserted both a structure and function for the compounds to be used in the claimed methods, there is not demonstration of a correlation between the two. However, as was indicated by the Federal Circuit, where a genus of inventions is claimed by function, there must also be provided some other characteristic of the claimed genus which correlates to the function such that those in the art would be able to identify the members of the genus. In view of the above, the application does not provide adequate written description support for the claimed inventions. Because the is inadequate support for the genera of compounds to be used in the claimed methods, there is also insufficient support to methods of using them.

Claim Rejections - 35 USC § 102

10. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

11. Claims 1-5, and 40 are rejected under 35 U.S.C. 102(a) as being anticipated by WO 97/43310 (of record in the June 2002 IDS). These claims have been described above. WO 97/43310 teaches the use of peptides comprising disclosed sequences for the treatment of HCV infections through the inhibition of the NS3 protease. See e.g., abstract. The reference teaches a method of administering the peptides to an infected individual. Page 3. Because the reference teaches that the peptides are effective for the inhibition of the NS3 protease activity, the peptides would also be required to come into contact with infected cells in the individual. Thus, the patent teaches methods of administering the disclosed peptides to an individual such that the peptides are provided to the infected cells.

Among the peptide inhibitors disclosed by the reference is a peptide comprising the NS4 sequence disclosed as SEQ ID NO: 21 on page 10 of the present application. WO 97/43310 document, page 10, SEQ ID NO: 11. This peptide also falls within the scope of peptides within the formula of Structure I of the present application. The reference therefore teaches the administration to HCV infected cells NS4 peptides comprising a sequence within Structure I. Because the reference teaches the administration of the same composition to the same patient population as the present claims, the disclosed methods would inherently perform the same functions. The reference therefore anticipates the indicated claims.

12. Claims 1-5, and 40 are rejected under 35 U.S.C. 102(e) as being anticipated by Zhang et al., U.S. Patent 5,990,276, also of record in the June 2002 IDS. The claims have been described above. Zhang provides similar teachings to the WO document disclosed above. See e.g., abstract, and columns 1, and 2-6. In particular, the patent also discloses the use of a peptide inhibitor

comprising a NS4A sequence and falling within Structure I. See, column 6, SEQ ID NO: 11. The reference therefore anticipates the indicated claims for the reasons indicated above with respect to WO 97/43310.

Claim Rejections - 35 USC § 103

13. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

14. Claim 1 is rejected under 35 U.S.C. 103(a) as being unpatentable over Bartenschlager (Intervirology 40:378-93) ion view of Pieroni et al. (J Virol 71:6373-80- of record in the June 2002 IDS). The claim has been described above. Bartenschlager suggests various targets for anti-HCV therapy. Abstract. The reference also states that "at least for some HCV isolates, removal of the NS2 region from the NS3 domain appears to be required for efficient processing of the NS3-5B region by the NS3 proteinase." Page 382. Thus, the reference provides suggestion for the inhibition of viral replication through targeting the cleavage of the NS2/3 protein.

Further, both Bartenschlager, and the Pieroni reference, identify protease inhibitors capable of inhibiting the removal of the NS2 protein from NS3. Bartenschlager, page 381; and Peironi, pages 6376-77. From these teachings, it would have been obvious to those in the art to inhibit the replication of HCV in infected cells through the administration to the cells of one of the inhibitors identified in the references. There would have been a reasonable expectation of success in such inhibition due to the teachings in Bartenschlager that removal of the NS2 region

is required for efficient processing of the remainder of the nonstructural regions of the polyprotein.

Conclusion

15. No claims are allowed. The methods involving the use of the elected peptide appear to be free of the art.

16. The following prior art reference is made of record and considered pertinent to applicant's disclosure. However, while relevant they are also not used as a basis for rejection for the stated reasons.

> Hijikata et al., J Virology 67: 4665-75- of record in the IDS of June 2002. This reference teaches that certain compounds were useful to inhibit cleavage by the Cpro-1 HCV proteinase- the proteinase responsible for cleavage between the NS2 and NS3 proteins in the HCV polyprotein. Page 4671. The reference is considered redundant to the teachings of Bartenschlager and Pieroni above.

17. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Zachariah Lucas whose telephone number is 571-272-0905. The examiner can normally be reached on Monday-Friday, 8 am to 4:30 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, James Housel can be reached on 571-272-0902. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Z. Lucas
Patent Examiner

James C. Housel 7/26/04

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